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DEPARTMENTS AND COLUMNS

Multicancer Early Detection Screening Tools: Not Economically Efficient, Not Ethically Equitable, Marginally Medically Effective

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A screening test for more than 50 cancers at earlier stages would strike many as a godsend. Such a test would promise, prima facie, to save 160,000 lives annually from a premature death from cancer, reduce the intensity of medical treatment, and reduce social costs. In brief, this is what is promised by the Galleri test. We will delineate those claims in greater detail and critically assess them from medical, economic, and ethical perspectives. We conclude, with many others, that this test lacks clinical validity and clinical utility. In addition, annual public funding of $100 billion for this test would be socially unaffordable; the opportunity costs would be unacceptable for both ethical and economic reasons. Further, the least well off with respect to cancer care would be made worse off if this test were publicly funded for everyone over the age of fifty.

Keywords: multi-cancer screening; equity; clinical validity; clinical utility; health care justice

Cancer researchers for several decades have had a vision of finding a non-invasive, accurate screening tool for finding cancers in the earliest possible stages when those cancers might be most curable. Such a screening tool would have to screen for numerous cancers since the alternative (screening for one cancer at a time) would be medically impractical and economically grossly inefficient.[1] The National Cancer Institute lists 158 types of cancer on its website.[2] A company called GRAIL has begun marketing a test called Galleri for $950 that it claims can detect more than 50 types of cancer with a simple blood test, often in the earliest stages of that cancer when a cure is most likely.[3] In addition, the test can correctly identify the tissue of origin for that cancer up to 92% of the time. Nothing else of comparable scope and accuracy exists at this writing as a screening test (late 2024).

The nationally recommended screening tests that currently exist in the United States are limited to breast, cervical, colon and lung cancer, the latter limited to high-risk patients. Those cancers represent about 25% of cancer cases in the United States, which means 75% of cancers lack a screening test, which means in practice that these other cancers are more often diagnosed at later stages that require more intensive and costly treatment that still results in 610,000 cancer deaths in the US annually. A test that can screen for more than 50 cancers at earlier stages would strike many as a godsend. Such a test would promise, *prima facie*, to save many lives from a premature death from cancer, reduce the intensity of medical treatment (and suffering) needed to treat many cancers, and reduce the cost to society. In brief, these are the broad claims made on behalf of the Galleri test. This essay is intended to delineate those claims in greater detail and then critically assess them from medical, economic, and ethical perspectives. We conclude, with many others, that this test lacks clinical validity and clinical utility.[4] In addition, public funding for this test would be socially unaffordable; the opportunity costs would be unacceptable for both ethical and economic reasons. Further, those who were least well off with respect to cancer care would be made worse off if this test were publicly funded for everyone over the age of 50.

Cancer: a statistical picture

In 2022, it was estimated that 1.9 million Americans were diagnosed with some form of cancer.[5] That does not include basal cell or squamous carcinomas, which are typically treated in a physician's office and not reported to any registry. Roughly 150,000 of those 1.9 million diagnoses were related to current screening protocols. That means about 1.75 million cancers were not caught through screening. Instead, patients presented with overt symptoms that proved to be related to a developing cancer. Note that 87% of cancers are diagnosed in patients over the age of 50. Roughly 610,000 Americans died of cancer in 2022.[6] The number of cancers diagnosed will increase steadily, likely through 2050, mostly related to the post WWII "baby boom" generation aging out. The projections to 2050 expect 2.3 million cases to be diagnosed annually.[7] Expected deaths will likely increase, but no precise number can be calculated due to expected advances in cancer treatment and diagnosis. What these statistics suggest is that there is enormous room for improvement regarding the early diagnosis of cancer. This is precisely what is promised by the GRAIL/ Galleri test, the primary virtue of which is that it is a simple blood test that seeks to capture circulating tumor DNA [ctDNA].[8]

The Galleri test: its nature and results

Two things are distinctive of the Galleri test as a screening tool. It can identify markers of more than 50 cancers in a patient's blood, and most often (85%–92% of the time) it can identify the location of that cancer. This test has the capacity to localize the cancer because it is seeking short fragments of ctDNA that are the result of tissue/tumor-related methylation of the DNA. Distinctive methylation patterns are characteristic of each organ in our bodies, which is why the test can localize most cancers that it detects. Note that the Galleri test is not a diagnostic test. It requires follow-up diagnostic procedures to confirm the presence of that cancer in that locale. Those diagnostic procedures may be invasive (a biopsy) or noninvasive (a CT, MRI, or PET scan). If all a screening test could tell us is that it shows evidence of cancer somewhere in our bodies, this would require considerable diagnostic work that would be costly and imply significant suffering and anxiety for many patients. The Galleri test would seem to reduce both the cost and the anxiety.

Keep in mind the distinction between cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA). Only a tiny fraction of cfDNA will be ctDNA. This has practical significance for screening. Advanced cancers, Stage III or IV, will deposit more ctDNA into the blood, but it will still be a tiny fraction of the cfDNA in the blood. A Stage I cancer will not deposit very much ctDNA into the blood, and consequently, detecting those very early cancers will be even more difficult. Galleri yields outstanding results in detecting Stage IV cancers (94% sensitivity), but that is not clinically very helpful. Detecting cancers at that advanced stage is extremely unlikely to yield a reduction in mortality, which is the point of doing the screening.

What are the projected results for Galleri?

What might be hoped for because of using something like the Galleri test to identify cancers at much earlier stages? One model was developed by Christina Clarke and Earl Hubbell, et al.[9] This model was then tweaked a year later (2021) by these same researchers.[10] Both these first authors are employees of GRAIL and Illumina (the company that owns GRAIL and manufactures the sequencers used by GRAIL for the Galleri test). In that 2020 article, the authors looked at 17 cancer types in individuals aged 50–79 using SEER data from 2006 to 2015. They imagined a hypothetical cohort of 100,000. They noted that 48% of all cancer deaths are attributed to Stage IV, and that 18% of all cancer diagnoses are at Stage IV. They contended that if all Stage IV cancers were diagnosed at Stage III, the result would be a reduction of 15% in all cancer-related deaths. In 2022, that would represent a bit more than 100,000 premature deaths averted. Further, the authors contend that if there were consistent downward stage-shifting across all cancers due to earlier detection, the result would be a 24% reduction in cancer-related deaths, which would be about 160,000 premature deaths averted using 2022 statistics. That 24% figure has been

contested by Ruth Etzioni et al.[11] They point out that in prior randomized screening for a specific cancer, no modality has been able to reduce the incidence of late-stage disease by even 50%. In breast cancer screening trials, the reduction in the incidence of late-stage disease was only 15%. Etzioni et al. suggest that they are willing to be generous and grant the Galleri test a reduction in the incidence of late-stage cancer by 25%, which would (in theory) result in preventing 6% of cancer deaths, not 24%. That would be about 36,000 averted deaths (in theory).

The reported Galleri statistics are astounding, but they are all based on a hypothetical model. The statistics and mathematical analysis may all be accurate, but the results have little to do with the real world. The correct way to read these results is in the hypothetical mode: If the Galleri test could match what this mathematical analysis suggests, this would represent (at least medically) the proverbial "game-changer" in a clinical setting. However, the only thing that really matters is what the Galleri test accomplishes in the real world with all the medical, personal, social, and economic complexity and uncertainty that is part of that world, including, most especially, the complexity of the 50 or more cancers that would be detected at various stages by the Galleri test.

In that 2021 article, the authors take essentially the same base SEER data as in the 2020 article. They contend that a suitable multicancer screening test could intercept 485 cancers per year per 100,000 individuals in the screened population, aged 50–79. The authors contend that this would result in an absolute reduction of 26% in cancer-related deaths per year, which would be about 160,000 averted cancer-related deaths. Again, these are astounding numbers, abstract, ethereal numbers, not actual numbers related to the implementation of something like the Galleri test. The authors note that roughly 33% of all cancers are diagnosed at Stage III or IV. Further, they contend that the test they have in mind could have a positive predictive value (PPV) of 30–40%, which is yet another astounding number. Again, analysis by Etzioni et al. concludes that a more reasonable figure for cancer deaths averted would be around 6%, not 26%.[12]

The next study we need to consider is the Circulating Cell-Free Genome Atlas Study (CCGA; NCT02889978). This was a case-controlled, prospective, observational study. The purpose of the study was to show that a blood-based multicancer early detection test [Galleri] using cell-free DNA sequencing in combination with machine learning could detect cancer signals from more than 50 cancers and identify in the vast majority of cases the origin of that cancer.[13] This substudy included 4077 participants: 2823 who had a cancer diagnosis and 1254 with noncancer status. The authors report overall sensitivity for cancer signal status at 51.5%. They note that sensitivity increased with stage: stage I: 16.8%; stage 2: 40.4%; stage III: 77.0%; stage IV: 90.1%. Eric Klein et al. contends that modelled data from this test "have shown that its use in the general population *could* shift cancer detection from Stage IV to earlier stages (I—III), *potentially reducing* cancer mortality."[14] The italics in the quoted passage are mine. They are there because these are hoped for results, which only a well-constructed trial in the real world could verify.

Some critical comments: prolonged empirical research is essential

Facts matter, ethically speaking. To be more precise, and for reasons spelled out in detail below, it would take a trial of at least 10 years in length to acquire the sort of data that would be necessary to establish the clinical validity and clinical utility of the Galleri test, most especially the stage-shift hypothesis. Recall that the basic assertion is that the ultimate result of using the Galleri test as a screening test would be a reduction in mortality. Shifting the detection of a cancer signal to an earlier stage may not guarantee that, especially if what we are detecting is an aggressive cancer to begin with, such as a pancreatic cancer. The Galleri test will identify a cancer signal at Stage I of pancreatic cancer 62% of the time.[15] However, that patient will still likely die of their pancreatic cancer because there is little therapeutic value and nothing of curative value for pancreatic cancer.

The natural history of pancreatic cancer is well known. The same is true in a very general sense for many other cancers, though there is considerable variability at the level of the individual patient regarding the evolution of their cancer, which is to say that it is difficult to know with confidence how much of a difference, if any, the Galleri test made regarding mortality. Perhaps for 20% of cancers

the natural history of the disease is well known. This is not true for the other 80%, which makes it very difficult to know with a high degree of confidence that identifying a cancer at an earlier stage made a significant difference regarding mortality. A lot depends upon what is available in the therapeutic armamentarium. We have numerous targeted therapies and immunotherapies for many cancers, but most of them yield only marginal benefits so far as life expectancy is concerned, typically months, or a year, not years.

To further clarify this last point, recall that the Galleri test had an overall sensitivity of 16.8% for Stage I cancers (much higher, as noted above, for more aggressive cancers resistant to being cured, but presumably somewhat lower for other cancers that would be very curable if they could be detected at Stage I). However, as some researchers have noted, a typical blood draw for the Galleri test is 10 mL. Nonaggressive tumors at Stage I will shed very little ctDNA. Most of the time that will be too little for current technology to capture that ctDNA. To increase the likelihood of identifying more ctDNA at Stage I would require increasing the quantity of blood taken for the test by tenfold.[16] This would be impractical and unaffordable, given a screening test available to 110 million Americans over age 50.

Recall that in any given year about 1.2% of this collection of 110 million Americans would be diagnosed with a cancer. Earlier, we called attention to the claim that if all Stage IV cancers were shifted down to being Stage III cancers, the result would be a reduction of 15% in cancer deaths. However, if we know nothing at all about a cancer other than that it is at Stage III, the likelihood of cure is about 40% at present (with wide variation depending upon numerous details regarding the genetic drivers of that cancer, the microenvironment of the cancer, and current therapeutic options). That would imply a more realistic *potential* reduction in cancer deaths of 6%. However, even that number might have considerable uncertainty attached to it. Cancer has proven to be extraordinarily wily in its ability to work around and defeat many of the targeted therapies and immunotherapies we are using today. Even for the more common cancers, there remains an enormous amount of basic science details related to cancer that we do not understand, such as the microenvironment that nourishes a cancer, or how some cancer cells hide within another cell. Robert Beckman et al. write: "In addition to tumor-centric intratumoral heterogeneity, tumors are known to feature tumor-centric epigenetic, transcriptional and signaling heterogeneity that may enable rapid adaptation of cancer cell populations. Importantly, this heterogeneity is further amplified by microenvironmental niches that will clearly differ from lesion to lesion."[17] For cancers that are rarer, the level of understanding, as well as therapeutic options, will be skimpy.

Apart from these basic science facts, all sorts of social, political, and economic considerations will constrain access to the available therapies that have varying degrees of effectiveness. It is reasonable to ask what good we would have done as a society to tell someone they have a stage II curable cancer but no ability to access that cure for financial reasons. Those patients will die of their cancers. Should Galleri be able to count those patients as "would have been cures, except for circumstances that were entirely beyond our control"? This would be an odd way of assessing the mortality benefits of the Galleri test in the real world.

The PATHFINDER study: a critical assessment

We next turn our attention to the PATHFINDER study sponsored by GRAIL.[18] This was a single-arm study that measured the time required to achieve diagnostic resolution after a cancer signal had been detected by the Galleri test. The study was also intended to determine the overall performance of the test, i.e., its positive-predictive value, incidence of false negatives and false positives. There were 6662 individuals who were tested, all of whom were over age 50. A cancer signal was detected in about 1% of this group. Results were presented at a meeting of the European Society of Medical Oncology [ESMO] in 2022.[19] A cancer signal was detected in 92 participants, of whom 35 participants were diagnosed with cancer. GRAIL emphasized that this represented a doubling of the number of cancers detected compared to other screening methods. The authors note that 25 of those 35 participants were diagnosed with a cancer for which no screening test was available, which would mean that the cancer was detected only with the appearance of symptoms, typically beyond stage I. For 73% of participants with a true positive

cancer signal, diagnostic resolution was achieved in less than 3 months. For those participants with a false positive signal, median resolution time was 162 days. The false positive rate was less than 1%, 57 out of 6652 individuals. That number might not be too frightening. However, GRAIL's goal would be to do annual screening of 110 million Americans over age 50, which would yield over 800,000 false positives with a median resolution time of 162 days. This is not a trivial outcome, either from a social perspective or the perspective of these individual patients.

Readers need to have a vivid image in mind of the implications of a false positive test. Physicians are now looking for something that really is not there, though they must believe it *could* be there. Recall that the Galleri test can report with 92% accuracy the tissue of origin. A radiologic scan is done to identify and verify that location. However, nothing is there, though the test yielded a positive signal. Perhaps it got the tissue of origin wrong (8% of the time). More radiologic scans are necessary to find something that is not there. To complicate matters, the scan might stumble on a benign tumor, which will require a biopsy to establish that the tumor is benign. For a patient, this means mounting anxiety as well as mounting financial costs. Patients might have very good insurance that still has substantial co-pay or deductible requirements. Patient anxiety might be relieved at the end of the day when their physician informs them that she *believes* the test result was a false positive, but many will feel cheated for having to pay for results that are essentially a mistake. Alternatively, should the physician say, "I believe the test result was a false positive. The radiologic scans we did found nothing. However, it is also possible there are tumors there that are just too small to be detected by these scans. We must just wait and see if anything develops." Those are not exactly comforting words. As a reminder, this outcome needs to be multiplied by 800,000 every year if the Galleri test is screening 110 million Americans. I can readily imagine the sale of anti-anxiety medications increasing dramatically because of such candid "assurances."

At this same ESMO conference, GRAIL also reported results of its real-world deployment of Galleri as a commercial test. That included 38,154 individuals which yielded a cancer signal detection rate of 1.1%. There were 326 patients with a positive cancer signal detection rate, and 108 cancers were confirmed in that group, as *voluntarily* reported by the ordering physicians. I emphasize the word "voluntarily" because this yields considerable uncertainty regarding the results of this screening procedure. Should we assume there were 228 false positives, i.e., nothing to report from the perspective of the ordering physicians?

However, another equally important point pertains to the number of false negatives that might have been part of PATHFINDER. This might not be something easy to identify, though that number is clearly relevant to the clinical validity and clinical utility of the test. To clarify, if someone presents to their physician 4 weeks after taking the Galleri test with symptoms that prove to be cancer, clearly the test missed that cancer (for whatever reason). The patient would have gone home thinking they were cancer-free after the test, despite a cancer history in the family. What if that cancer is identified symptomatically 3 months, or 6 months, or 1 year after the Galleri test? Should all these count as instances of false negative results?

To be sure, participants offered the Galleri test are told that a negative result does not necessarily mean that they are cancer-free. The test will miss some cancer signals. Are participants given some precise numbers to understand this? As noted above, across all cancers the sensitivity of the test will be 16.8% for a stage I cancer. What that means is that the test will miss 83.2% of stage I cancers. The test will have 40% sensitivity for Stage II cancers, again, across all cancer types detected by the test. That means the test will miss 60% of Stage II cancers. Again, the sensitivity of the test for more aggressive cancers at Stage I or II, such as pancreatic cancer, will be much higher. That might be seen as good news. However, the primary reason the test is more sensitive regarding those cancers is that they are shedding more ctDNA because they are an aggressive cancer. The bad news is that most of those cancers will remain incurable, even if they are detected at Stage I or II.

I remind the reader of another contextual point. For any given cohort of 110 million Americans over age 50 who take the Galleri test, only 1.2% will have a cancer that in theory could be detected by that test. That means that 98.8% of participants taking the test will be truly negative (though 0.8% of those individuals will be given a false positive test result). Only a very tiny fraction of participants who receive a negative test result will be false negatives. For some participants, knowing this statistic will be comforting.

For others, it may prove to be a source of anxiety since no one will know who among all those negatives are in reality false negatives. Further, as things are now, roughly half of all patients who are diagnosed with cancer symptomatically are diagnosed at Stage I or II, which means most of these patients will be cured of their cancer. Consequently, a false negative diagnosed later symptomatically as Stage I or II will not necessarily be a death sentence.

Some personal stories

A personal story might be useful at this point. This is the story of Anthony Arenz, a 51-year-old firefighter in Arizona.[20] He was offered a free Galleri test, paid for by the city of Mesa, because firefighters (given the nature of their work) are at elevated risk for some cancers. Mr. Arenz's test was negative. But he was also offered a free MRI, which he was reluctant to bother with because of the negative Galleri test. He did take the MRI, which showed he had a stage I kidney cancer that the Galleri test had missed. Another firefighter, Mike Curtis, was worried about cancer. His father had died of cancer at age 58. He took the Galleri test and got a positive result. His physician, Dr. Vershalee Shukla, had doubts about that result and did several radiologic diagnostic tests which showed no signs of cancer. This was a false positive, which had precipitated considerable anxiety in Mr. Curtis. Dr. Shukla reviewed 6300 first responder Galleri tests and found a sensitivity of only 6.7%, which means the test missed 93% of the cancers that were there. In addition, she found that the positive predictive value of the test was less than 50%.[21] GRAIL's own data confirmed this, which showed in PATHFINDER a positive predictive value of 38%. What this means is that 62% of the time that a positive result from Galleri is recorded, it is wrong. But it must be proven wrong, which means some number of radiologic scans or other tests are needed to establish that fact. That can represent costs of several thousand dollars which may or may not be covered by an individual's health insurance. It also means, as noted above, a mean of 162 days to establish that the positive result was false.

More critical analysis: uncertainty, excessive cost, injustices

We now turn to a broader critical assessment of the Galleri test. Three very large issues: enormous uncertainty regarding the validity and utility of the test itself, the aggregated social cost of the test, both by itself and in relation to the validity and utility of the test itself, and issues of health care justice, i.e., whether the use of this test as a broad screening tool represents a just use of limited health care resources compared to all other potential uses for those resources.

What counts as robust evidence: PATHFINDER 2?

Patricia Deverka et al. suggest that what is necessary is having "robust evidence" regarding the validity and utility of the test itself.[22] That generates several more follow-up questions. What would count as evidence that was "robust enough"? Is GRAIL willing to forego marketing this test aggressively until that evidence is "robust enough"? Or does GRAIL believe that the evidence they have so far is sufficiently robust that they are justified in recruiting the National Health Service in the United Kingdom to provide the test to 140,000 British citizens over the age of 50? And is the test "robust enough" to justify at least 15 major medical centers in the United States partnering with GRAIL to make the test available to their patient population through their physician partners? Finally, is the relevant patient public willing to wait patiently for access to the test until the evidence is "robust enough?"

We noted above that several clinical researchers affiliated with GRAIL are suggesting based on their models that 140,000 to 160,000 lives could be saved every year in the US if this broad cancer screening were done. I would have to concede that evidence of that magnitude would certainly constitute robust evidence of clinical validity and utility. However, that is just a hypothetical number, a very uncertain hypothetical number depending upon the reality of the assumptions built into that model. Actual

evidence would require a decrease of 160,000 cancer deaths per year clearly linked to the use of this test. Most researchers will say that it will take at least 10 years before that number is verified or falsified.[23] As we will see below, considerable technical detail is associated with assessing the validity and utility of the test right now. This is not a detail that the broad public can readily understand, and they might not be willing to understand it either. The simple message that Grail is presenting, along with its many clinical partners, is this: "We have a simple blood test that can identify more than 50 different cancers, as well as their location in your body, at the earliest possible stage when cancer is most curable." That is a seductive message, followed by: We need to tell you that some medical and scientific researchers, as well as greedy insurers, are unwilling to authorize this test for broad dissemination unless every "i" is dotted and every "t" is crossed in accord with the most elegant requirements of research. They estimate that it might take 10 years for that to be accomplished. That represents 1.6 million lives lost to cancer that did not need to be lost. You need to write to members of Congress to put a stop to this nonsense. Demand that Medicare fund the cost of this test. This test costs only $950. A year of targeted cancer therapy could cost $200,000, and the patient still dies. Tell Congress to stop wasting taxpayer dollars and sacrificing lives for the sake of "robust evidence."

Some readers may feel that this last constructed quote is just rhetorical exaggeration. However, as comments to the referenced article show, the British public is extremely supportive of what they see as the life-saving potential of the Galleri test.[24] Likewise, consider the quoted passages below, as reported by the BBC in the UK. These are ordinary folks who were asked whether they endorsed the proposal by GRAIL to provide the Galleri test to 140,000 British citizens. These folks were hypercritical of researchers who expressed the view that maybe the broad dissemination of the Galleri test was not such a good idea.

> "This is great news, no ifs or buts - great news - hope they make big progress on Alzheimer's next. All the doubters and conspiracy theorists - do one! These are people making a difference, you aren't." [Sounds like they would make me the next Socrates…….drinking the tainted wine!!!!]

> "My lung cancer was detected late, so it was already at stage 3B (out of 4) when it was discovered. The worst conversation of my life was the one with the consultant starting "I'm afraid it's too late to cure your cancer, but we will try to manage it for as long as we can…" If a blood test can catch cancers before they get to that stage, it can only be a good thing. I really hope this test works."

> "This is brilliant news. If successful, will the NHS have the foresight to offer it to everyone? It must be cheaper than the billions spent on cancers which are undetected for too long not to mention the number of lives which could be saved."

If I were the CEO of GRAIL, I would be very pleased with these results. This is essentially a "work around" of any critical assessment of the Galleri test by appealing to public support for the test. GRAIL has now undertaken in the United States with its 15 medical center partners another clinical trial labeled PATHFINDER 2 (NCT05155605). It will recruit 20,000 participants over 18 months and follow them for 3 years. These are all individuals over age 50 who have had no sign of cancer for the past 3 years. It is a single-arm interventional trial. What is being assessed is the performance of this test in detecting a cancer signal among individuals who would have no reason to believe that they had a cancer. We will look at this trial more critically below. For now, we want to just assess the optics as they might be used by GRAIL. Specifically, it is likely at least 100 cancers will be detected that are true positives. Those individuals may not be happy to be told they have a cancer, but assuming it is stage I or II, they will feel blessed that it was detected early, and it would likely be curable. As CEO of GRAIL, I would want to capture that reaction for a television or web commercial. That would speak to the hopes and fears of most Americans over age 50. That commercial would be used to encourage ordinary citizens to urge Congress to pass the *Medicare Multi-Cancer Early Detection Screening Coverage Act.*[25]

Why should we think there was anything problematic about the PATHFINDER 2 study? It will detect some early cancers that may be cured. That seems like a clear social good. However, the whole point of this screening test is to reduce the incidence of death from cancer. These patients are only being followed for 3 years. A small number might die within that 3-year window. The fate of the rest of these individuals would be unknown to the researchers. Will this tell us anything with confidence regarding the number of lives that were saved from a death from cancer? I believe the short answer is "No."

In theory, more than 50 different cancers could be detected among these 20,000 individuals. Of course, it is very unlikely that would happen. The number of cancer signals detected would likely be about 1.2%, roughly 240 cancer signals. That is too few to expect to find 50 different cancers. Further, even if a much larger test did detect those 50 different cancers, the natural history for most of those cancers would be unknown. That makes it extremely difficult to know confidently that this screening effort resulted in saving a life that otherwise would have been lost.

Uncertainty and the natural history of cancers

Recall all the literature today regarding precision medicine. What has become very clear over the past 15 years is that cancer is extraordinarily complex and wily, i.e., capable of surviving all manner of attacks with chemotherapy, targeted therapies, and immunotherapies. This is explained by the genetic heterogeneity of many cancers and the evolution of cancer drug resistance. Any tumor might have one genetic driver with other potential drivers of the cancer. This is what is called intratumor heterogeneity. But there is also genetic heterogeneity among the tumors that are supposed to comprise *the same cancer*. This makes it even more difficult to know the "natural history" of any given cancer.

Why would it be important to know the natural history of a cancer? Knowing the natural history makes it easier to know the effects of either a screening intervention or a therapeutic intervention. To illustrate, the natural history of some specific cancers may mean that a cure is beyond the capabilities of any treatment today. Thus, it might typically be the case that cancer will present with symptoms at Stage III. The Galleri test might identify that cancer at Stage I, what we referred to earlier as stage downshifting. However, detecting that cancer earlier makes no difference regarding the actual outcome for that patient. It might create false hope in that patient. The reality is that that patient will be a cancer death statistic at some point in the future. In other words, this does nothing to justify the claim that Galleri will be able to reduce the number of cancer deaths per year by 160,000.

Another noteworthy point is that many cancers are identified symptomatically at Stage I or Stage II, and many of those cancers will be cured. Galleri might identify them as well. However, Galleri cannot then claim credit for saving those lives because those lives were going to be saved anyway through current clinical practice. A critic might ask whether it *really matters* if those lives are saved because of current clinical practice or because of the Galleri test. The short response is that it does matter. Again, recall that GRAIL wants to provide this screening test annually to 110 million Americans over age 50 at a cost of more than $100 billion per year to someone. This is a cost on top of everything we currently do by way of diagnosing a cancer. To justify such a huge expenditure, we would have to *know in the strongest possible sense* that this test would be responsible for saving more than 100,000 lives from a premature death from cancer every year. PATHFINDER 2 will provide virtually no evidence to justify that conclusion.

What evidence is needed to support that conclusion? It would likely take at least one million patients who would have the Galleri test annually for 10 years with follow-up for all those patients, especially those with a cancer signal for 10 years beyond that, or a total of 20 years to get potentially helpful results.[26] To be realistic, there is no guarantee that we will get the result that we would hope for. We might save fewer than 10,000 patients for each of those years.

Galleri: The financial challenges

As noted above, there is growing political pressure for Congress to fund through Medicare the cost of providing the Galleri test to all Medicare recipients, which would add roughly $55 billion to the annual

cost of the Medicare program. It would take at least 10 years to develop a robust enough evidence base to justify Medicare funding. The political argument will be made that tens of thousands of Medicare patients will die every year while waiting for sufficient evidence to accrue. This should be seen as an obviously self-serving, disingenuous argument because the authors of this argument are claiming (in effect) that they *know* all those lives will be lost when in fact that is what needs to be proven.

One strategy for addressing this problem is to use an available Medicare strategy, *coverage with evidence development*. This has been used with several extraordinarily expensive cancer therapies that present with mixed evidence of effectiveness. However, the cost in those situations might be $2–3 billion annually. The cost in this case would be $55 billion per year, or $550 billion over a 10-year period. This would not be a prudent choice, nor would it be a just use of limited health care resources. At the very least, the opportunity costs would have to be considered. Medicare officials would have to ask whether more lives could be saved at a lower cost per life if that $55 billion were redirected to other therapeutic interventions with greater certainty regarding the desired outcome.

Medicare could also cut that $55 billion cost in half by doing a rigorous scientific gathering of the necessary evidence, i.e., a double-blind study. In other words, half the Medicare population would be in the experimental group receiving an annual Galleri test, the other half would be in the control group receiving the present standard of care, i.e., waiting until cancer symptoms presented in a clinical context, then being treated for that cancer. This would be a very hard sell, politically speaking. In fact, it might be more accurate to say that it would be an impossible sell. The Medicare population would likely revolt and demand that everyone has access to the Galleri test. The fear of cancer is really that deeply engrained.

Another alternative would be for Medicare to limit the tested population to one or two million Medicare recipients for that 10-year period. This too would be a political non-starter. How would those individuals be chosen? Would individuals with a family history of cancer be given preferential access to that study? Or would it be a lottery that included all Medicare recipients? A lottery would be presumptively fair, no one would be getting any special treatment. However, the political rhetoric would call attention to the fate of the 95% of Medicare recipients who were not included in the lottery, who were being potentially condemned to an ugly death from cancer.

If Medicare were to provide coverage to all their recipients, the pressure would be placed on private insurers to cover the test as well. The political demand would be that this be done immediately in order to prevent the loss of those 160,000 hypothetical lives researchers from GRAIL have suggested could be saved every year. In effect, what this would mean in practice is that we (taxpayers and insurance premium payers) would bet a trillion dollars for that 10-year period that we would save 1.6 million lives. What if we lose that bet? What if we can confidently prove with sufficiently robust evidence that we saved only 10,000 lives each year? That is the real ethical and economic question that needs to be asked and answered.

If we go back for a moment to the issue of the robustness of the test, it sounds like we are talking about a simple test that yields clear, meaningful results. However, Deverka et al. point out: "There is no established evidentiary framework for payers to apply to a multicancer test assessment where the sensitivity of the test varies by cancer and by stage, so the benefits and harms of screening vary by tumor type."[27] In other words, payers (you and I as taxpayers or insurance premium payers) would have no idea what we were paying for or whether it was worth paying for that in the first place. Further, how is this supposed to affect the clinical encounter? What should the process of informed consent look like before the test is administered?

Galleri: The healthcare justice challenges

I now want to turn to several ethics' issues, mostly matters of healthcare justice and resource allocation. GRAIL has claimed the ethical high ground by contending that the virtue of their proposal is that everyone is covered, i.e., no social inequities. This is obviously a self-serving use of this ethics rationale. However, we will assume that public political pressure has resulted in the approval of social funding (public and private) aimed at providing the Galleri test to all 110 million Americans over the age of 50.

Recall that this is a screening test, not a diagnostic test. If 2.4 million Americans generate a cancer signal each year, then all manner of diagnostic tests will be required to identify and verify the existence of that cancer. There would be no guarantee that all those individuals could afford the cost of the diagnostic follow-up. Again, roughly 800,000 of those cancer signals will be false. It would be safe to say that likely 30% of those individuals could not afford the costs associated with those diagnostic tests (no insurance, high co-pays or deductibles, little in the way of savings). Is that unjust? If they have an established cancer that will now grow, they will likely die from that cancer. Further, even if they can afford whatever diagnostic tests are necessary, the therapies necessary to treat their cancer may be completely unaffordable for many of these patients. They will forego those therapies and accept their fate. Is that an unjust outcome or an unfortunate outcome? It would clearly be an unfortunate outcome if, given the genetic characteristics of their cancer or the location of the cancer (intimate portions of the brain), nothing could be done. But it seems very different, ethically speaking, if a therapy is available, maybe significantly life-prolonging but not curative, but the cost is entirely unaffordable for that patient. These are all lives that will be lost prematurely. Where do those lives "fit" when GRAIL is touting the efficacy and ethical virtue of the Galleri test? Those lives, statistically and abstractly speaking, would have been saved if various financial barriers did not prevent those abstract figures from becoming real. We noted earlier that if the Galleri test was available annually to 110 million Americans, then perhaps 36,000 lives would be saved from a cancer death. That figure must be reduced by at least 33% to account for the financial barriers that would prevent many of these patients from accessing the effective therapies that are available. The phrase that has been introduced into the cancer medical literature over the past 10 years is the "financial toxicity" associated with extremely costly cancer treatments today.[28]

There are some hidden or invisible injustices that would be built into the Galleri proposal. The prior paragraph suggested that no one would have to pay for the Galleri test; it would be a social subsidy. However, economists will readily point out that the money that pays for those tests is not manna from heaven. It is money from everyone who pays the Medicare/Social Security tax, or who is paying health insurance premiums directly, or indirectly through foregone wages. In effect, the poor and working poor are paying for that test just like everyone else. The ethically significant difference is that they are deriving little in the way of substantive benefit from the test, especially if the test yields a positive cancer signal. The ultimate objective of the test is to detect cancer at any earlier, treatable, curable stage. This is not a benefit that will be enjoyed by those unable to afford those treatments. However, they will still be partially subsidizing the cost of the diagnostic treatments and tests for everyone else since that is part of what they are paying for with their Medicare taxes/premiums or private insurance premiums. It seems clearly unjust that the financially less well-off should be helping to subsidize the treatment costs of those who are much better off financially.

We should also mention the inequities associated with the social determinants of health. Certain racial/ ethnic groups will have a higher incidence of various cancers and be further down in the economic spectrum. Mexican farmworkers (undocumented) would be one such example. They are underpaid for their work, do not have health insurance for the most part, are exposed to long periods in the sun (melanoma) as well as some number of toxic chemicals used to treat crops that are associated with a range of cancers.

Would the injustices mentioned above disappear if there were no social funding for the test, if it were entirely a matter of an individual's ability to pay each year for the test that determined who would have access to the test? The top 20% of Americans income-wise could likely pay for the test each year from their own pockets. Assuming the test yields some of the lifesaving benefits GRAIL contends it offers, that would yield some life-prolonging advantages for these individuals compared to everyone else who was financially less well off. Everyone else would have to be satisfied with our current practices regarding the diagnosis and treatment of cancer. How unfair is that? The short answer is that there would still be some residual injustice. After all, individuals in that top 20% who had a positive cancer signal would need all sorts of diagnostic follow-up along with whatever recommended therapy was available. They would have paid for the test itself from their own pocket, but all these other costs would either be paid for by Medicare or some form of private insurance. Those who were financially less well-off would again have helped to subsidize those costs. This is regrettable, though we are a liberal society. That is, we would have no

politically acceptable reason for banning access to the test for those who could afford it. No one is made directly worse off because of allowing the relatively wealthy to pay for the test from their own pockets. However, that is not the end of the story.

Galleri as low-value care

Is the Galleri test an instance of "low-value" care? What counts as low-value care? Should we not be funding (socially) low-value care? I have written extensively about what I refer to as the "Just Caring" problem.[29] In brief, it states that we have only limited resources (money we are collectively willing to spend on health care) to meet unlimited health care needs. Those needs are unlimited because constantly emerging new medical technologies effectively create new medical needs. Investors in GRAIL might be inclined to say that we "need" the Galleri test in the morally valenced sense of need. But they are speaking from the perspective of their financial self-interest. Every other investor in other new medical technologies will say the same thing. Still, the bottom line is that we cannot afford everything in the way of new medical technologies, especially if the technology is of low value and deserves low priority. What makes a technology of low value is that it delivers only marginal benefits, often with a high degree of uncertainty, at excessive cost relative to any likely benefit. Most policy analysts would say that aducanumab, that recent Alzheimer's drug, would be a clear instance of low-value care.[30] It was initially priced at $56,000 per year and would be available to at least two million AD patients in the early disease stages. It would yield a temporary marginal gain in cognition. The aggregated cost to society would be $100 billion per year. How does Galleri compare to that?

Galleri "only costs" $950, but it would be provided each year to 110 million Americans, thereby generating a $100 billion expenditure. What benefit will it provide? For 98 million individuals, it would inform them they do not have any detectable cancer. That is a benefit, except that they would have gone into taking the test believing that they did not have cancer. However, the additional claim is that the test might save 24,000 lives from a death from cancer each year (though I remind the reader this is a hypothetical number to which significant uncertainty ought to be attached). For the sake of argument, we will accept that number as real. Part of the argument for Galleri is that it will save both lives and money. Let us do some math. If each of those 24,000 individuals would have needed $100,000 worth of last year of life cancer care, perhaps with one of those targeted therapies, that represents a savings of $2.4 billion. However, there are 800,000 false positive tests generated every year, discussed above. Those need to be resolved. A very conservative estimate of the cost of resolving each of those false positive results would be $5000. That represents an aggregated cost of $4 billion, which more than negates the hypothetical savings associated with saving those 24,000 lives. That represents a net increase in total annual costs of another $2 billion. Still, someone will say that human life is priceless, that a just and caring society is ethically obligated to spend that $100 billion to save those 24,000 lives. However, no one really believes human life is priceless unless they expect that it will be someone else's money that will be used to save or prolong a life, most especially their own life.

How many cancer patients cannot afford the cost of their cancer treatments, which they forego? The short answer is 25%.[31] That would be about 180,000 of the 610,000 patients who die of their cancer each year. That suggests this critical question: Would it not be more just and caring, ethically obligatory, to spend that $100 billion on the effective cancer treatments needed by those 180,000 individuals, which would be a very concrete, verifiable substantive good instead of spending that money on anxiety relief for 108 million Americans who are told that the Galleri test could find no evidence of cancer in them this year? Certainly, this looks like a higher value use of those healthcare dollars. Spending the money in this way would save more lives and more life-years than the hypothetical 24,000 lives that might be saved by the Galleri test.

Another larger critical question needs to be raised, though we cannot address it in this essay. This pertains to the challenge of "onco-exceptionalism."[32] In brief, critics of much of precision medicine call attention to the exceptionally high costs of most of these targeted therapies and immunotherapies and the marginal benefits generated for most of these patients. In other words, the gains in life expectancy

(these are metastatic cancer patients) are most often measurable in months, sometimes a year or so. Only a small percentage of these patients gain extra years of life from these therapies. The term "onco-exceptionalism" is a pejorative term intended to call attention to the belief that cancer is deserving of unlimited funding relative to all the other life-threatening degenerative conditions that might afflict older individuals. This is not a defensible view. The larger question we must ask is this: If we as a society are willing to provide $100 billion additional healthcare dollars every year to meet the healthcare needs of the elderly, then how high a priority should the Galleri test, and all the various cancer therapies out there now for late-stage cancers, have relative to all the noncancer health care needs and therapies that are out there to meet these other health care needs?[33] This is not a question we can answer in this essay. This is a question, I have argued, that ought to be left to a process of fair and inclusive rational democratic deliberation among the elderly themselves, and among the rest of the population that expects to become elderly but might have costly healthcare needs in the present. In this larger context, it should be abundantly clear that the Galleri test would have, and should have, very low priority from an ethical perspective, i.e., the perspective of a just and caring society with limited health care dollars.

Notes

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   Readers need to keep this figure in mind since this death reduction was accomplished without the benefit of the Galleri test. See Rebbeck TR, Burns-White K, Chan AT, Emmons K, Freedman M, Hunter DJ, et al. Precision prevention and early detection of cancer: fundamental principles. *Cancer Discovery* 2018;**8** 7):803–11. Prevention was one key factor here, most especially related to smoking and persistent emphasis on breast cancer screening and self-examination. Cancer treatments would be responsible for only a relatively small percentage of those averted deaths. The other statistic we want to keep in mind is that 68% of patients diagnosed with some cancer in 2022 will not die of their cancer. Therefore, we will see a steady increase in the number of cancer survivors in the US, from about 17 million in 2022 to 22 million in 2030. Some readers may feel that number ought to

be higher. However, cancer is largely a disease of older individuals, with 28% of cancers being diagnosed among those over age 75. This suggests that many individuals will die of other diseases associated with advanced age.

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However, Grail provides links on their website to connect consumers to telemedicine prescribers and laboratories where they can have their blood drawn. See note 23, Rubin 2024.

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